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PATENT
Docket No. 300622004600

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Ruth M. Saskowski

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the application of:

Rajesh S. GOKHALE, *et al.*

Serial No.: 09/500,747

Filing Date: 9 February 2000

For: METHODS TO MEDIATE POLYKETIDE SYNTHASE MODULE EFFECTIVENESS

Examiner: Kathleen M. Kerr

Group Art Unit: 1652

Official received 10/24/02 K. Kerr

SUPPLEMENTAL RESPONSE

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

This response supplements the response to an Office action herein mailed 12 February 2002, which was responded to 12 August 2002. Applicants greatly appreciate the opportunity offered by the Examiner to supplement this response without the need for an intervening Office action indicating the omission of a response to the rejection in paragraph 21 of this Office action. The then-pending claims, claims 23-39, were rejected for lack of enablement; while applicants responded to the 35 U.S.C. § 112, paragraph 1, rejection of these claims on the basis of written description, applicants did not specifically address the enablement aspect of this rejection.

As applicants understand this rejection, the issue is mostly related to the operability of constructs that would include elements other than those associated with DEBS modules. There

enablement rejection, it is believed that the comments set forth in regard to written description are applicable here. In that response, applicants pointed out that they had enclosed a declaration of Chaitan Khosla demonstrating that one of skill in the art could readily identify the linkers in any naturally occurring PKS. The relevant nucleotide sequences for a number of PKS are known in the art and those that are known demonstrate that there is sufficient homology in the catalytic domains that the linker regions can be readily identified as those between the catalytic domains, even though the linkers themselves do not display a high degree of homology.

However, the bulk of the rejection appears to be focused on operability. The Office questions whether the linker regions, once identified, can be utilized with all molecules from any modular PKS. The Office states that the limited homology of the linker regions does not support broad generality; in the context of enablement, applicants assume the Office is questioning whether linkers, once identified, will be operable with heterologous catalytic domains.

Respectfully, it is not clear to applicants why the Office postulates that linker domains from one modular PKS would be inoperable to transfer the growing polyketide chain between catalytic domains of a different modular PKS. What applicants have shown in Examples 1 and 2, is that, unexpectedly, if a substrate is to be processed by a module that expects the substrate to come from a domain to which it is covalently bound, that substrate cannot be supplied from the medium unless an N-terminal portion of an intermolecular linker (ERL)is supplied; that linker will now allow the catalytic portion of the module to function as if it were normally one which would accept a substrate from the medium, rather than from an upstream portion of protein which contains, itself, a catalytic module. Example 3 shows that the intramolecular linker (RAL) that normally conducts the chain from module 1 to module 2 can equally catalyze the transition from module 1 to module 3 or to module 6 which are covalently linked through this linker to module 1. Example 4 shows that this same RAL can facilitate transit between erythromycin module 1 and rifamycin module 5. Example 5 demonstrates, again, that rifamycin modules can be substituted for erythromycin modules with the appropriate

linkers. Essentially, the catalytic domains of rifamycin module 5 are substituted for the catalytic domains of module 2 of erythromycin.

As stated in the examples, the expected triketides or polyketides are formed in these cases. Examples 4 and 5 thus demonstrate that there is interchangeability with respect to the appropriate linker regions in terms of their capability to provide access by polyketides to heterogeneous catalytic domains.

The Office states that there are "no controls" in these experiments; however, it is unclear to applicants what sort of controls would be necessary. Either the triketide or polyketide is produced or it is not. If it is produced, as it is in these examples, then the experiment is successful. Applicants respectfully request further explanation of what sort of controls would be required in order to validate these results.

Thus, in summary of the argument so far, applicants believe they have answered the question with regard to identification of the appropriate regions in the context of their response to the written description; applicants have shown in the specification that the constructs claimed are capable of effecting the synthesis of polyketides and are thus useful and find nothing, so far, in the rejection, which would support the concept that the invention would not work as described based on any documentation or scientific theory. Given these factors, applicants respectfully suggest that the Office has not met its burden of showing a reason to doubt the operability of the hybrid modular PKS constructs claimed.

The other element of the rejection is that the teachings Tang, *et al.* (members of the group to which the present inventors belong) "demonstrate that combinations of modules from different PKSs (pikromycin, erythromycin, and oleandomycin) without the use of ERLs as Applicants **[sic]**." Applicants assume that what is meant here is that Tang shows it is not necessary to provide the linkers that are provided in the constructs claimed, and that the constructs would work even if no precautions with regard to linkers were taken. Respectfully, regardless of the accuracy of this interpretation of the findings of Tang, *et al.*, it is not seen how the successful

operability of constructs other than those claimed reflects on the operability of the claimed constructs themselves.

Tang, *et al.*, showed that the first two proteins in the picromycin PKS in combination with the separately expressed third protein subunit of the erythromycin PKS cooperated successfully to obtain a hybrid polyketide. Evidently, the Office interprets this to mean that there is no effective ERL between subunit 2 of picromycin PKS and subunit 3 of the erythromycin PKS. This is not necessarily so, since another explanation would be that the C-terminal portion of the ERL of at least one PKS can communicate with the N-terminal portion of an ERL from at least one different PKS. Similar results were found when the oleandomycin third subunit was substituted for the erythromycin third subunit.

In any event, the operability of such constructs does not appear to demonstrate, in any way, that the constructs claimed by applicants would not be operable.

For completeness, applicants call the attention of the Office to an isolated failure of the system recorded on page 81, right-hand column. It is not believed that this isolated instance is anything other than the exception that proves the rule.

Thus, in summary, applicants respectfully suggest that the data set forth in the application are supportive of the scope claimed and that there has been no contrary evidence offered by the Office. The ability of constructs other than those claimed to produce operable results is irrelevant to the operability of the claimed constructs. Accordingly, withdrawal of this basis for rejection is also respectfully requested.

Again, applicants are very grateful for this opportunity to complete their previously filed response. The willingness of the Examiner to expedite prosecution in this way is genuinely appreciated. If there are further matters that might be resolved by telephone, a telephone call to the undersigned is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to

charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 300622004600.

Respectfully submitted,

Dated: October 25, 2002

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From: Kate H. Murashige

Date: October 25, 2002

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Title: METHODS TO MEDIATE POLYKETIDE SYNTHASE MODULE EFFECTIVENESS
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SIGNATURE OF APPLICANT, ATTORNEY OR AGENT

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